Questions and Answers on Data Monitoring Committees issues

Biostatistics working party, especially
Peter Volkers, PEI
Steven Teerenstra, Radboudumc / CBG-MEB
Kit Roes (chair BSWP), Radboudumc / CBG-MEB
Armin Koch, MHH

European Medicines Agency, Methodology, Data Analytics and Methods Task Force, especially,
Ina-Christine Rondak
Frank Pétavy (workstream head)

Disclaimer

Apart from presenting (shortened versions of) the verbatim text of the Q&A, statements in this presentation are my own and do not necessarily represent the opinion of BSWP or EMA.

Context

- Draft published August 2018
- Public consultation August 2019
  - comments from 10 stakeholders
- Q&A was officially adopted by CHMP on 17 September 2020

The Q&A is not a standalone document but should be read in conjunction with the DMC guideline.

- GCP IWG is planning to revise the DMC guideline, after CHMP agrees to that

Principles DMC

- Independent members, external to the Sponsor
- evaluating/monitoring accumulating data with an objective to safeguard safety of current and future participants, and progress of the trial
- Advisory role to the Sponsor (regarding modification, continuation, termination)
- Maintain trial integrity and credibility (as DMC may have access to unblinded data)

Questions on:

- Decision power of DMC
- Communication by DMC
- Disagreement between DMC and Sponsor representative on stopping the trial
- Need for (non-)DMCs in early development

Decision power

Advisory principle ===> decision power

Question	Answer (shortened)
1. Are **DMC recommendations binding** for a Sponsor?	No. However, not following DMC recommendations should be documented and justified.
2. Can a **DMC stop a study**?	No. Of the DMC and the Sponsor, only Sponsor can stop study.

Advisory + trial integrity principle ===> decision power

Question	Answer (shortened)
3. Can a **DMC change study design aspects** (e.g. increase sample size, drop treatment arms)?	No. Of the Sponsor and DMC only the Sponsor can change design aspects Preplanned changes (e.g. adaptive designs): Operationalize such that the DMC can maintain its advisory role • without making direct decisions and can maintain trial integrity • DMC may look at unblinded data, but Sponsor should be kept blinded (DMC could 'help out' to execute a properly pre-planned decision-rule, but in principle this could also be another independent committee.) Unplanned changes: Can be proposed by DMC, but such that trial integrity is maintained.

Communication

trial integrity principle+ advisory role ===> communication

Question	Answer (shortened)
4. Is a **direct communication** and exchange of information **between competent regulatory authorities and a DMC** possible?	As a general rule: no, communication via Sponsor. • DMC is advisory • Sponsor final responsibility In exceptional circumstances (public health threats) affecting the conduct current trial or other trials, competent reg.auth. may need information of the DMC: • Sponsor should be involved in request for exchange • If possibility that trial can continue: Exchange from DMC to reg.auth. directly to preserve trial integrity (not breaking the blind) If reg.auth. wants to inform DMC of safety concern: via Sponsor
5. Is a **direct communication between Ethics Committees and a DMC** possible?	In some nations, Ethics Committees monitor specific AE, risk/benefit, and can change/stop a trial. This combination of knowledge and decision power may give risk of introducing bias. Therefore, same principles as above.

trial integrity principle ===> communication

Question	Answer (shortened)
6. Should the **Investigators be informed** about the outcome of DMC meetings?	Yes. DMC can communicate the following* 1) Continue without changes 2) Continue with modifications: a) Quality improvement measures b) Measures for safety/negative risk-benefit: - patient care - patient recruitment 3) Stop the trial Trial integrity preserved if 1), 2a) or 3). For 2b) communication should be such that trial integrity is preserved as much as possible *if recommendation adopted by Sponsor

safeguard safety ===> communication

Question	Answer (shortened)
7. **When** shall **competent regulatory authorities be notified** of DMC outcomes?	Unexpected safety finding: immediately. Other outcomes: together with planned safety/interim analysis reporting.

Disagreement DMC vs Sponsor’s trial steering committee on stopping

trial integrity ===> reconcile disagreement

Question	Answer (shortened)
8. **How** should the **DMC proceed when contemplating the recommendation to stop the trial**?	Minimize impact on trial integrity as trial might still continue, Applies to • Degree of involvement Sponsor • Communication to investigators 1) When DMC is considering recommending stopping - Recruitment on hold and involve external experts - DMC and experts discuss in closed sessions all evidence in and outside the trial 2) Should DMC recommend stopping and Sponsor's representative disagrees - All efforts from both sides to reconcile 3) If not resolved in 2), then - Closed session with DMC, external experts and senior Sponsor personnel with decision power and independent of the trial - Reach common decision Important to present a common decision as otherwise trial integrity damaged (operational bias)

(non-)DMCs in early phase trials

trial credibility + safety protection

Question	Answer (shortened)
9. When is there a **need for a DMC in early development phases**? *(Combines answer to question "Do **DMC members** have to be **external** in relation to the Sponsor **in early development phases**?")*	• Sponsor's product knowledge may be needed in early phase safety monitoring => (some) non-independent members in an safety monitoring • Trial credibility => sufficient independent members for objective decision making • non fully independent safety monitoring committee are not called DMCs, but different: e.g. safety review committee • (Also) installing a DMC can still be in interest of sponsor, as early development may include complex and possibly controversial decision making. E.g. in case of unexpected / critical findings that require objective, but not urgent decision making, a DMC can provide (additional) assessment that enhances credibility of the decision making.